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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/229,283	01/13/1999	DAVID E. FISCHER	48012	7211

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RONALD I. EISENSTEIN
NIXON PEABODY LLP
100 summer street
BOSTON, MA 02110

EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/229,283	FISCHER, DAVID E.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,4,13,14,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,4,13,16 and 17* is/are rejected.

7)☐ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 28, 2004, the supplemental response submitted October 28, 2004, the response filed December 29, 2004, the Declaration and Amendment filed January 10, 2005 in response to the interview of December 21, 2004 are acknowledged and have been entered. Claims 16-17 have been added, claims 2-3, 5-12 and 15 have been canceled and Claims 1, 13, 16 and 17 have been amended. An action on the RCE follows.

2 Claims 1, 4, 13-14, 16-17 are pending and currently under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 14, line 5. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

New Grounds of Rejection

Claim Rejections - 35 USC 112

5. Claims 1, 4, 13, 16-17 are rejected under 35 USC 112, first paragraph because the specification, while enabling for a method for screening for melanoma which comprises immunohistochemically contacting a biological specimen with an antibody which selectively recognizes the amino terminal Taq-Sac fragment of

human microphthalmia does not reasonably provide enablement for a method for screening for melanoma which comprises contacting a biological specimen with an antibody which binds to human microphthalmia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to an immunohistochemical method for screening melanoma comprising contacting a biological specimen with an antibody which binds to Mi and determining whether Mi is expressed in the specimen by antibody binding to Mi, wherein said binding is indicative of Mi expression and wherein the expression of Mi in a malignant cell is indicative of melanoma. This includes any antibody that binds to microphthalmia and that cross reacts with any protein that comprises epitopes found in microphthalmia.

The specification teaches that determining the origin of a metastatic tissue arising from a melanoma is extremely difficult (p. 2, lines 8-9). The ability to determine the origin of a metastatic disease is very important because it can affect the diagnosis and/or type of treatment regime prescribed and a more accurate means for diagnosing melanoma is important (p. 2, lines 13-18). Microphthalmia (Mi/MITF) is a transcription factor implicated in pigmentation, mast cells and bone development (p. 5, lines 19-21). The inventors have discovered that there is a high correlation between the presence of Mi in a malignant cell and that cell being melanoma (p. 6, lines 29-31). Mi is a sensitive and specific marker for melanoma. The specification teaches monoclonal antibody D5, raised against a histidine fusion protein expressed from the amino terminal Taq-Sac fragment of human MITF cDNA of Tachibana et al, of record, which is specific for Mi, but not related proteins (p. 14, lines 25-30). Further, polyclonal antibodies to the same His fusion

appear to have been generated and have been shown to not be cross reactive on DNA mobility shift assays (para bridging pages 16-17). Mi antibodies generated against the N-terminus Taq-Sac fragment of human Mi expressed as His-fusion were shown not to cross react with other b-HLH-ZIP factors (para bridging pages 17-18) and did not cross react with TFEB, TFEC or TFE3 (p. 14, lines 25-30). Histopathology on human melanoma tissue was performed using antibody D5 to Mi (p. 20, lines 10-15).

One cannot extrapolate the teaching of the specification to the scope of the claims because the broadly claimed antibody is not selective for Microphthalmia. The specification clearly teaches that antibody to the amino terminal Taq-Sac fragment does not cross react with other b-HLH-ZIP factors, in particular does not cross react with TFEB, TFEC or TFE3. Although the Fisher Declaration specifically states that there is very little difference between the amino acid sequences of the known Mi isoforms and that antibodies that are being successfully used for screening do not distinguish between the Mi forms, neither the specification, as originally filed, nor the Declaration provide any teaching as to which sites, other than the amino terminal Taq-Sac fragment are useful for producing antibodies that will function as claimed, that is for the screening for melanoma, wherein the binding of the antibody in a malignant cell is indicative of melanoma. In particular, Weilbaecher et al (J. Exp. Med., 1998, 187:775-785) as well as Hemesath et al (Nature, 1998, 391:298-301) emphasize the concerns expressed in the specification concerning cross-reactivity wherein they specifically teach that Mi antibodies, useful for identifying Mi, were generated against the amino terminus Taq-Sac fragment of human Mi expressed as a His-fusion and that these antibodies were shown not to cross react with other b-HLH-ZIP factors (p. 4

of 22 of Weilbaecher et al and 4 of 7 of Hemesath et al). In addition, Weilbaecher et al specifically teach that microphthalmia is a Myc-related bHLH-ZIP protein (see p. 2 of 22). Given that the bHLH-ZIP proteins are a related family of proteins, it would be expected that at least a subset of antibodies against Mi would cross react with other bHLH-ZIP proteins, as specifically noted in the specification and in Weilbaecher et al. Since microphthalmia is a Myc-related bHLH-ZIP protein, this cross reactivity would of course include cross reactivity with Myc. This cross reactivity is of critical importance to the claimed invention as it is well known in the art that Myc protein is expressed in a wide variety of cancer types. For Example, Oda et al (Histopathology, 2001, 39:629-63) specifically teaches that c-myc expression, in secondary malignant giant-cell tumor of the bone, was detected by immunohistochemistry (see abstract and Table 2, p. 634); He et al (Zhongguo Gonggong Weisheng (2001), 17:675-677) specifically teaches that immunohistochemical staining revealed c-myc expression in lung cancer samples (see abstract); Su et al (Zhounghua yi xue za zhi, 1995, 75:144-146) specifically teach that c-myc protein is expressed in hepatic tumors as revealed by immunohistochemistry (see abstract). Further, a review of the literature revealed that a novel ASPL-TRE3 fusion is found in two distinct human cancers, a lethal sarcoma of uncertain lineage and a unique subset of pediatric renal adenocarcinoma. This fusion replaces the N terminal portion of TFE3 by the fused ASPL sequences which retaining the DNA-binding domain of the TFE3 transcription factor. Preliminary transactivation and subcellular localization data support the function of ASPL-TFE3 as a transcription factor associated with malignancies of both mesenchymal and epithelial derivation (see Ladanyi et al, CRISP 5R01CA095785-03, Summary). In view of the above, it appears that

bHLH-ZIP proteins are expressed in a variety of cancers. Given the broadly claimed antibody that binds, it is not clear how one could predictably screen for melanoma by the binding of an antibody that would be expected to cross-react with other bHLH-ZIP proteins, and thus is not selective for microphthalmia. Given the expression of other bHLH-ZIP proteins in a broad range of cancer types, it could not be predicted that the binding of the broadly claimed (and thus cross reactive) antibody would in fact be indicative of melanoma. The selectivity of the binding antibody appears to be of critical importance to the claimed invention as the issue of cross reactivity was specifically addressed in both the specification as originally filed and in the Weilbaecher et al and Hemesath et al references. The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed antibody that binds would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

6. Claim 14 appears to be free of the art but is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. No claims allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Susan Ungar
Primary Patent Examiner
March 16, 2005